Monograph

No 1

Good Laboratory Practice

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MONOGRAPH No.1

FOREWORD BY THE CHAIRMAN OF ECETOC

It is my pleasure to introduce the first monograph to be published by ECETOC.

The purpose of this document is to contribute to the discussion of a topic which affects not only industry and its many laboratories, but which can also play a role in the wider context of improving the protection of human health and our environment.

Why should ECETOC consider itself competent to disseminate views on Good Laboratory Practice ?

There are a number of reasons, perhaps the most important being that we represent a large proportion of those chemical companies in W. Europe which have laboratory facilities for, and expertise and experience in, testing and evaluating chemicals for health and environmental effects. Not only are we deeply concerned that the standard of such work shall be high, but in assessing what the standards should be in practice we can draw on outstanding experience, from the very conception of a product through to its manufacture, use and disposal.

We accept the need for good standards, but are also more aware than most that unnecessarily restrictive standards could damage scientific innovation, the development of science and the motivation of our scientists. For a continual improvement in the protection of health and the environment, insofar as they are affected by chemicals, we need to ensure a continual improvement in the sciences of toxicology and ecotoxicology. Regulations on GLP which hinder this improvement will defeat the common overall objective of both industry and the regulatory authorities.

A. Robertson

GOOD LABORATORY PRACTICE

I - GENERAL

A. WHAT IS GLP ?

Industry and the regulatory authorities are increasingly concerned with studies for assessing the possible hazards to health and the environment arising from the manufacture, use and disposal of chemicals. GLP comprises a set of standards for the conduct of such (non-clinical) laboratory studies, and is intended to ensure the quality and integrity of the data obtained from them.

These studies will often include the measurement of physico-chemical properties, and tests for toxicity and environmental effects. Their design, conduct and documentation have much in common and it is appropriate that they should be covered by one set of GLP regulations.

At present, only the US Food and Drug Administration's GLP has passed into law. Other proposals are at the discussion stage and therefore still permit an exchange of views between industry and the regulatory authorities.

B. THE PURPOSE OF GLP

Speaking about laboratory testing and GLP, the Food and Drug Administration Commissioner has stated that «Decisions about the safety of ... products, based wholly or in part on data derived from testing, are too important for the agency to accept anything less than the best scientific data that can be obtained». «Conformity with these rules (i.e. GLP) is intended to assure the high quality of the non-clinical laboratory testing required to evaluate the safety of regulated products».

GLP standards are thus intended to ensure the quality and integrity of test-data submitted as the basis for regulatory decisions on chemicals. Sound GLP standards will ultimately contribute to improved protection of health and the environment.

C. THE SCOPE OF GLP

As generally understood, GLP concerns HOW laboratory studies are carried out, monitored and recorded, but not WHICH tests and test protocols are chosen. The rules apply only to non-clinical laboratory studies carried out :

— to predict and assess the possible adverse effects of a chemical on health and the environment, including physico-chemical measurements for the adequate identification of the chemical in this context ;

— for submission in a petition for registration or re-registration of a regulated chemical.

Tests such as exploratory safety studies, range-finding (dose) experiments and the development of analytical methods, which are not intended for such submission, are excluded; as are studies with human subjects, clinical studies or field trials.

All laboratories (industrial, university, contract and government) carrying out testing for the above purpose will be subject to Good Laboratory Practice.

D. THE HISTORY OF GLP

The need to improve laboratory practice was first recognised in the US during 1975. The FDA found that some data presented to it on the health effects of chemicals were deficient in certain important respects, and subsequent inspection of a number of testing laboratories, including its own, revealed faults needing rectification. For example :

1. Some experiments were poorly conceived and executed, or inaccurately analysed and reported.
2. Some technical personnel were not sufficiently aware of the importance of adhering to the test protocol, and of the need for the highest possible accuracy in such work.
3. Some managements did not ensure that a critical review of data and proper supervision of personnel were carried out.
4. In some cases the qualification and training of personnel were not adequate for their tasks.
5. Instances were found of a lack of proper animal care and data management procedures.

Although many laboratories worked conscientiously, the US authorities concluded that the problem required legislatory action in the form of GLP regulations to prevent future deficiencies, and the first proposals were made by the FDA in 1976 (Federal Register, vol. 41, No. 225, Nov. 19, 1976, pages 51206 et seq). After taking public comments on the proposals the regulation was finally published as law in the Federal Register, Vol. 43, No. 247, Dec. 22, 1978, pages 60013-60020. The Environmental Protection Agency (EPA) later issued the first in a series of GLP proposals for testing to be carried out in compliance with the Toxic Substances Control Act - see Federal Register, Vol. 44, No. 91, May 9, 1979, pages 27362-27375. The Agency intend to issue further proposals to cover testing for environmental effects, and physico-chemical measurements. The Interagency Regulatory Liaison Group exists to harmonise FDA and EPA proposals.

The FDA regulations had an impact on non-US laboratories, since chemical manufacturers exporting to the US have to satisfy US requirements concerning test data. Legislation concerning the safety of chemicals is not, of course, confined to the United States, and for example, the text of the European Communities' 6th Amendment to the 1967 Directive on Classification, Packaging and Labelling of Dangerous Substances calls for test data on new chemicals and requires that «Execution of the tests shall be in conformity with the principles of good current laboratory practice». Some member states of the EEC are now examining proposals for GLP on a national basis. Thus there is a need for international recognition or harmonisation of GLP, and in 1979 a group within the OECD Chemicals Testing Programme was formed to recommend an internationally acceptable form of GLP.

At the time of writing, the question of GLP is very much the subject of international debate.

E. ECETOC AND GLP

ECETOC is an organisation of about 40 W. European chemical companies including almost all of the larger ones and many of the medium sized — see Appendix 1. It is concerned with the scientific aspects of toxicity and ecology. Although the current way of life in industrialised countries has been made possible by modern technology, which includes a massive contribution from the chemical industry, it is clear that desirable advances in the technology and scale of operations should not present unacceptable risks to human health and the environment. Therefore one of ECETOC's aims is to organise, pool and use the scientific knowledge, experience and expertise of its members so that a better scientific contribution can be made to the protection of health and conservation of the environment. This requires the promotion and application of good science, especially toxicology and ecotoxicology.

In studying the possible health and environmental effects of their products, chemical companies have a vital interest in working to good standards themselves, and in being sure that contract laboratories to which they put out work do likewise. Much of the past work in this area has been carried out by the chemical industry which has to concern itself with the health and environmental effects of its products from their conception, through development and production to their eventual marketing, use and disposal. As a consequence it has a range and depth of experience second to none. The increasing volume of future testing, especially under regulatory requirements, will continue to be carried out mainly by, or under control of, the industry.

Thus, because of its members' interest in the promulgation of good practicable GLP standards, and its competence to put forward views based on the scientific experience and ability of its members, ECETOC appointed a group of responsible and practising scientists from member companies to draw up a set of GLP recommendations. These are intended to serve as a contribution to the international discussion. A list of the scientists responsible for the recommendations, and of the Scientific Committee of ECETOC which approved them, is given in Appendices 2 and 3.

F. THE ECETOC GLP PROPOSALS

These are given in full at the end of this Monograph.

1. Criteria

   Any GLP proposals have to meet certain criteria:

   a) They must be effective in the basic aim of ensuring the quality and integrity of test data.

   b) They must be sensible in practice and allow for some differences of laboratory organisation and management between different organisations and countries.

   c) They must be necessary and sufficient, i.e. detailed enough to be unambiguous and achieve their purpose, but not so over-detailed and constrictive as to prevent the full deployment of scientific initiative, experience, expertise and judgement. Toxicity and ecotoxicity testing are rarely routine operations, and to obtain valid experimental results and conclusions therefrom requires considerable scientific skill and initiative.

d) The principles must be sufficienty in line with existing proposals to permit future harmonisation or mutual recognition across national boundaries.

e) They must not add unnecessarily to the cost and administrative burden on those responsible for testing, and should impose the minimum of non-productive, bureaucratic work on trained personnel and management.

f) They should be so worded as to cover the measurement of physico-chemical properties, and tests on environmental effects as well as health effects, since these are all included in the existing or proposed regulatory requirements for testing chemicals.

In accord with the fourth criterion given above, the FDA regulations on GLP were taken as a basis. Their framework offered a good systematic approach to the problem, and much of the text enshrined practices which were clearly desirable, and indeed were already followed in many laboratories. They were at the time the only legally established set, and had considerable force as a precedent.

A number of other documents, mostly at the proposal or discussion stage, were available and were also taken into consideration.

2. Divergencies from FDA proposals

There are various reasons why certain changes, omissions or additions were made to the FDA document in arriving at the ECETOC proposals. Some of the FDA proposals were too elaborate and burdensome, and were not necessary in achieving the desired aim. Others would impose a too-detailed organisation and structure on a laboratory. Some of the subject-matter was specific to the US, or was inappropriate for GLP since it would normally be the prerogative of other government authorities. Finally, the FDA regulations are concerned only with health effects, and in order to cover the measurement of physico-chemical properties and environmental effects various changes of wording and additional words or phrases were necessary.

a) Major differences

- Quality Assurance. The FDA section 58.35a) coll for a «QA Unit composed of one or more individuals» to monitor the compliance of the study with GLP regulations. The obligatory creation of such an entity would impose an organisational structure on a laboratory which may not be suitable. Smaller laboratories would find this particularly difficult, expensive and wasteful of skilled man-power. ECETOC prefers to concentrate on meeting the aims of QA, and not on the organisational mechanism for achieving them, by requiring a set of procedures and controls for this purpose, designed and operated as best fits the particular laboratory — see ECETOC GLP sections A.2.h. and B.4 below.

- Periodic inspection. In section 58.35, 3), FDA requires inspections by the QA unit within a testing facility «at intervals adequate to assure the integrity of the study» for studies lasting less than 6 months. For studies of over 6 months, it requires inspection every 3 months. ECETOC prefers the former approach for all studies, since the periodicity of inspection, to be adequate, depends very much on the type of study and developments within it — see ECETOC GLP, section B.4 a), i).

- Master schedule sheet. In section 58.35 b.i.) the FDA requires the maintenance of a «master schedule sheet of all studies in the testing facility». ECETOC agrees that this is a good practice in planning and managing a laboratory, but it is also aware that such sheets have been asked for during inspections by regulatory authorities. It is not proper that one inspecting authority should be entitled to know of work being carried out for submission to another authority, and we have therefore avoided the term «master schedule sheet» and have adopted a form of words (section B.1.a) which has no implications regarding the inspection process.
- Synthesis and process details. The FDA in section 58.105.a) requires documentation of methods of synthesis or fabrication of the test substance, for the purpose of characterising it. ECETOC believes that it is not necessary to reveal such information, since the substance will be adequately characterised by other information called for, e.g. source, identity, composition, etc... Impurities arising from the laboratory synthesis or plant manufacture will normally be identified as required, without having to divulge the method of synthesis or manufacture.
- Study Director's responsibility. In FDA section 58.33, the Study Director is to have overall responsibility for : «... the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting.»

  In such multi-disciplinary studies as are necessary in this field, no one person would be expert enough to carry immediate responsibility for the detailed interpretation, analysis, documentation and reporting, and ECETOC prefers a more realistic description i.e. : «responsible for the overall conduct and reporting of a study ...» (see section II, B.3.b.).

b) Minor differences

These are too numerous to list in full. They often involve careful wording and the avoidance of repetition to produce a shorter, clearer text. In a few instances, the obligatory nature of a requirement has been softened by making it «as necessary», where a mandatory requirement is not necessary to achieve the aim of Good Laboratory Practice. One example of a simplification which removes a cumbersome requirement concerns signature of the final report. The FDA in section 58.185 a) 12), requires that the final report shall contain the signed and dated reports of each of the individual scientists or other professionals involved in the study. In a multi-disciplinary study this would involve a large number of people. The ECETOC proposal recognises normal line-management responsibilities and requires only «the principal scientists from each of the cooperating disciplines» to report and sign — see : ECETOC GLP J.1 a) v).

c) Omissions

The FDA sections on inspection (58.15) and disqualification (subpart K) of testing facilities have been omitted since these will presumably be regulated by national authorities. FDA section 58.53 dealing with office space, showers, toilets, etc... is also governed by existing national legislation and is not appropriate to GLP rules. Finally, the requirement (53.29f) that sick personnel report their health or medical condition to their immediate supervisors is not proper practice in many European countries, and has been omitted.

G. THE INTERNATIONAL DEBATE

In the Spring of 1979, ECETOC presented its proposals to the Commission of the European Communities and discussed the rationale on which they were based. The document was also presented via individual ECETOC members to a number of national governments. The reception was generally favourable, and the fact that the industry had worked to present a reasonable and useful set of proposals was appreciated. The ECETOC paper was later tabled at the first meeting of the OECD Group on GLP, and will be among the major documents on which subsequent discussions are based in an attempt to achieve internationally recognised rules.

The international situation on GLP was made significantly more complicated when in May 1979, the EPA issued GLP proposals (for discussion) to cover toxicity testing carried out under the Toxic Substances Control Act — see Federal Register, May 9, 1979, pages 27362 to 27375. While the basic proposals were at first glance close to those of the FDA, substantial differences were revealed by a closer reading. In particular, the EPA declare that they intend to issue further proposals to cover tests relevant to «chemical fate and ecological effects» (p. 27363, col. 2), and may propose more specific regulations pertaining to particular effects or particular chemicals (p. 27363, col. 1).

ECETOC deplores the proposed multiplication of GLP regulations in a series of separate documents, and the tendency to confuse GLP with test protocols — see comments on the scope of GLP in section C above. Such procedures will make compliance with GLP extremely complex and cumbersome, and represent a significant obstacle to international harmonisation.

ECETOC hopes that its proposals will serve as a useful basis for harmonisation, and will continue to work with all concerned for the recognition of soundly-based and practicable GLP standards which achieve their ultimate purpose of helping to protect health and the environment without putting any unnecessary and wasteful burdens on those responsible for testing.

II. — GOOD LABORATORY PRACTICE - THE ECETOC PROPOSALS

(the lettering of sub-parts follows that of the FDA for convenience of comparison)

SUB-PART A : GENERAL

A. 1. SCOPE

The standards for GLP will be applied to all non-clinical experimental studies carried out in relation to a submission of data on safety, with respect to health and the environment, of substances subject to regulation.

A. 2. DEFINITIONS

a) The Non-clinical Experimental Study (henceforth called the study) means any **in vitro** or **in vivo** experiment in which a test substance is examined to evaluate its safety regarding health and the environment.

b) Test Substance means a defined substance, mixture or formulation which is under investigation.

c) Control and Reference Substance means any defined substance, mixture or formulation used to provide a basis for comparison with the effects of a test substance.

d) Batch means a specific quantity of a test, control or reference substance possessing uniform character and produced during a defined cycle.

e) Test System means any animal, plant, microbiological, cellular, subcellular, chemical or physical system used to provide an evaluation of hazards to health and the environment.

f) Sponsor means a person(s) or entity who commissions and/or supports the study and/or is responsible for submission of the resulting data to the regulatory authorities.

g) Testing Facility means the operational unit(s) where the study is being conducted.

h) Study Director means any scientist or other professional person of appropriate education, training and experience who is responsible for the overall conduct of the study.

i) Quality Assurance Programme means that set of procedures and controls designed to ensure the quality and integrity of the study, in compliance with good laboratory practice.

j) Raw Data means all original records and/or documentation, including verified copies thereof, which are the result of the original observations and activities in a study and are necessary for the reconstruction and evaluation of the report of the study.

k) Specimen means any material derived from a test system for examination or analysis.

SUB-PART B : ORGANISATION AND PERSONNEL

B. 1. TESTING FACILITY MANAGEMENT

Testing facility management shall a) maintain a schedule of all studies carried out ; and for each study shall :

b) Designate a Study Director as described in B.3, before the study is initiated.

c) Replace the Study Director promptly if it becomes necessary to do so during the conduct of a study, record the action, and maintain it as raw data.

d) Assure that there is a quality assurance programme as described in B.4.

e) Assure that test, control and reference substances have been appropriately tested according to section F.1 or F.3, as applicable.

f) Assure that personnel, resources, facilities, equipment, materials and methodologies are available as scheduled.

g) Assure that personnel clearly understand the functions they are to perform.

h) Assure that any deviations from these regulations reported under the quality assurance programme are communicated to the Study Director, and that corrective actions are taken and documented.

B. 2. PERSONNEL

a) All persons engaged in the conduct of, or responsible for, the supervision of a study should have education, training and experience adequate for the tasks required of them.

b) The testing facility should maintain a summary of qualifications, training, experience and a job description for each professional or technical person concerned.

c) There should be a sufficient number of personnel for the timely and proper conduct of the study according to the protocol.

d) Personnel should observe sanitary working practices and health precautions necessary to minimise risk to themselves and with respect to the integrity of the study.

e) Any person having a health or medical condition that may have an adverse effect on the quality or integrity of the study should be excluded from operations or functions at risk from such an adverse effect.

B. 3. STUDY DIRECTOR

a) For each study a scientist or other professional of appropriate education, training and experience shall be designated by management as the Study Director.

b) The Study Director will be responsible for the overall conduct and reporting of the Study and for implementation of the approved Study Plan, including any authorised changes.

c) In conjunction with other specialists, as appropriate, he will ensure that procedures are designed and operated so as to assure that the study is performed in accordance with the study plan.

B. 4. QUALITY ASSURANCE PROGRAMME

a) There shall be procedures for assuring that the facilities, equipment, personnel, methods, practices, procedures, and records conform with Good Laboratory Practice, and for assuring the reliability and integrity of data obtained from a study. The quality assurance procedures shall be carried out by a person or persons designated by management and not responsible to the Study Director, and shall involve :
   i) Periodic inspection and auditing of a study to assure compliance with Good Laboratory Practice.
   ii) Prompt reporting to the Study Director and management of any problems likely to affect the integrity of a study.
   iii) Submission to the Study Director and management of written reports on the Quality Assurance inspections and audits of each study at appropriate intervals.
   iv) Reviewing of final study reports to assure that each report accurately describes the methods, procedures and observations, and that the reported results accurately reflect the raw data of the study.
   v) Preparing and signing a statement to be included with the final study report which shall specify the dates when inspections were made and findings were reported to management and to the Study Director.

b) A written description of the Quality Assurance programme and a record of all audits performed, but excluding details of findings and problems as well as actions recommended, shall be maintained as in sub-part J.3.

c) Any work performed by a contractor shall be subject to a Quality Assurance programme agreed between the sponsor and contractor.

SUB-PART C : FACILITIES

C. 1. GENERAL

The testing facility shall be of suitable size, construction and location to meet the requirements of the study and minimize disturbances that would interfere with the study. The design of internal parts of the testing facility shall provide an adequate degree of separation of the different functions or activities to assure the proper conduct of the study.

C. 2. TEST SYSTEM FACILITIES

a) The testing facility shall have a sufficient number of rooms or areas to assure the separation of test systems and the isolation of individual projects when necessary.

b) Suitable facilities shall be available for diagnosis, treatment and control of diseases within the test system.

c) Facilities shall exist for the collection and disposal of all wastes and refuse from the test system. Disposal facilities shall be provided and operated so as to minimize vermin infestation, odours, disease hazards, and environmental contamination.

d) There shall be storage areas as needed for feed, bedding, supplies and equipment. Storage areas for feed and bedding shall be separated from areas housing the test systems and shall be adequately protected against infestation and contamination. Refrigeration shall be provided for perishable supplies or feed.

C. 3. FACILITIES FOR HANDLING TEST, CONTROL AND REFERENCE SUBSTANCES

a) As necessary to prevent contamination or mix-ups, there shall be separate areas for :
   i) receipt and storage of the test, control and reference substances ;
   ii) mixing of the substances with a carrier, e.g. feed ;
   iii) storage of mixtures.

b) Storage areas for the test, control and reference substances or mixtures shall be separate from areas housing the test systems and shall be adequate to preserve the identity, concentration, purity and stability of the substances and mixtures.

C. 4. LABORATORY OPERATION AREAS

a) Separate laboratory space shall be provided, as needed, for the performance of the routine and specialised procedures required by the study.

b) Separate space shall be provided for cleaning, maintaining and, if necessary, sterilizing equipment and supplies used during the course of the study.

C. 5. SPECIMEN AND DATA STORAGE FACILITIES

Space shall be provided for archives, with access limited to authorized personnel only, for the storage and retrieval of all data and specimens from completed studies.

SUB-PART D : EQUIPMENT

D. 1. EQUIPMENT DESIGN

Equipment used for generation, measurement, or assessment of experimental data, and for controlling environmental factors relevant to the study shall be suitably located, and of appropriate design and adequate capacity to function according to the study plan.

D. 2. MAINTENANCE AND CALIBRATION OF EQUIPMENT

Equipment used in a study shall be adequately inspected, cleaned, maintained, tested, calibrated and/or standardised according to the standard operating procedures and/or study plan. Records of such routine or non-routine work shall be maintained.

SUB-PART E : TESTING FACILITY OPERATION

E.1. STANDARD OPERATING PROCEDURES

A testing facility shall have written and approved standard operating procedures that are adequate to ensure the quality and integrity of the data generated in the course of the study. Deviation from these standard operating procedures shall be authorized by a competent person as designated by management, and documented as raw data in the study.

Each separate laboratory area shall have immediately available standard operating procedures relevant to the activities being performed there. Published text-books and articles, manuals and directions may be used as supplements to these standard operating procedures.

A historical file of standard operating procedures and revisions thereof, including the dates of such changes, shall be maintained as in sub-part J. 3.

Standard operating procedures, where applicable, shall describe but not be limited to the following:

a) Test, control and reference substances (henceforth called substances)
   - i) Receipt, identification, characterisation, handling, formulation and storage of substances.
   - ii) Testing the homogeneity and stability of substances, and concentration of substances in mixtures with carriers.
   - iii) Administration of substances.

b) Test system
   - i) Room preparation and external conditions for the test system as appropriate.
   - ii) Procedures for receipt, transfer, proper placement, characterisation, identification and care of test system.
   - iii) Test system observations and examinations.
   - iv) Laboratory tests and analyses.
   - v) Handling of individuals within the test system found moribund or dead during the study, where applicable.
   - vi) Termination of an experimental study and/or necropsy of the test system.
   - vii) Collection, identification and handling of specimens.
   - viii) Histopathology.

c) Equipment
   - i) Use of equipment.
   - ii) Maintenance, cleaning, calibration and/or standardisation.

d) Documentation, evaluation and reporting
   - i) Data collection, handling, storage and retrieval.
   - ii) Preparation of reports.

E.2. REAGENTS AND SOLUTIONS

All reagents and solutions which are used in a study shall be labelled to indicate identity and, where appropriate, concentration or titre, expiration date, and storage conditions or special precautions.

E. 3. HANDLING OF TEST SYSTEMS

a) If necessary, test systems received from outside sources shall be placed in quarantine to assess their health status. This assessment shall be in accordance with the usual veterinary or other appropriate practice.

b) If, during the course of the study, treatment of disease or suspected disease is necessary, this may be carried out provided that such treatment does not interfere with the study. The diagnosis, authorization of treatment, description of treatment, and data concerning treatment shall be documented and retained as raw data.

c) All information needed to specifically identify individuals or groups within a test system shall appear on the container or housing of that system.

d) Warm-blooded animals, excluding suckling rodents, used in laboratory procedures that require manipulations and observations over an extended time, or in studies that require the animals to be removed and returned to their home cages for any reasons (e.g. cage cleaning, treatment, etc...) shall receive appropriate identification (e.g. tattoo, toe clip, colour code, ear tag, ear punch, etc...).

e) Different test systems shall be housed in separate rooms when necessary. Similar test systems used in different studies should not ordinarily be housed in the same room when inadvertent exposure to test, control or reference substances, or test system mix-up, could affect the outcome of the studies. If such mixed housing is necessary, adequate differentation by space and identification shall be made.

f) Test system cages, racks, tanks or other accessory equipment shall be cleaned and sanitised at appropriate intervals. If any pest control materials are used, the use shall be documented. Cleaning and pest control materials that interfere with the study shall not normally be used.

g) If necessary, feed and water used in a study shall be analysed periodically to ensure that contaminants known to be capable of interfering with the study, and reasonably expected to be present in such feed or water, are not present at levels above those specified in the protocol. Documentation of such analyses shall be maintained as raw data.

h) Accessory materials used in a study shall not interfere with the purpose or conduct of the study, and shall be changed as often as necessary.

SUB-PART F : TEST, CONTROL AND REFERENCE SUBSTANCES

Documents related to the source, analysis, stability, mixing and accountability of test, control and reference substances (henceforth called substances) are to be retained as raw data for a period as specified in sub-part J. 3.

F. 1. CHARACTERISATION OF SUBSTANCES

a) Each substance shall be identified by a name and/or code number, as well as by a batch number, by which its source can be traced. Before use in the study, the identity, composition, concentration or other characteristics appropriately defining the substance shall be known. A sample of each batch of substance shall be retained as in sub-part J. for studies lasting four weeks or longer. Data relating to these characterisations shall be retained as raw data. Commercially available products shall be characterised by name, code or other appropriate information.

b) The stability of the substance shall be determined as relevant to the study. If this information is not available at the start of the study, such information shall be generated during the course of the study, and maintained as raw data.

c) The substance shall be so stored that deterioration is kept to a minimum. The storage container(s) shall be identified with a name or code, and carry the batch number and, if necessary, the expiration date and the substance-specific storage conditions.

F. 2. HANDLING OF SUBSTANCES

a) A procedure for the handling and storage of substances shall be established such that :
   i) changes in the properties of a substance on storage are minimized ;
   ii) contamination or mix-ups are excluded.

b) A procedure for accounting for quantities of substances received, distributed, used in studies and returned shall be established. Records, including dates and quantities, shall be maintained as raw data.

F. 3. MIXTURES OF DEFINED SUBSTANCES WITH CARRIERS

a) When it is necessary to mix, dilute, suspend or dissolve the defined substance with a carrier for administration to the test system, appropriate procedures shall be established :
   i) to determine the homogeneity in mixtures, if appropriate ;
   ii) to determine the stability of the defined substance when mixed with the carrier ;
   iii) to determine periodically the concentration of the defined substance in the carrier.

b) If it known that the defined substance or carrier, or the combination, has a limited shelf-life, the earliest expiration date shall be shown on the container.

SUB-PART G : PLANNING AND CONDUCT OF A STUDY

G. 1. STUDY PLAN

For each study, a study plan shall exist in a written form prior to initiating the study and must contain, but not be limited to, the following information :

a) A descriptive title which reveals the nature and purpose of the study.

b) Identification of the test, control or reference substance by name and/or code number.

c) The name of the sponsor, and the name and address of the testing facility or facilities.

d) The name of the Study Director.

e) The proposed starting and completion dates of the study.

f) The justification for selection of the test system.

g) Characterisation of the test system. Where applicable, the organisms' species, strain, substrain, source of supply, number, body weight range, sex, age, and other pertinent information with respect to the test system.

h) The procedure for identification of the test system.

i) Detailed information on the experimental design, including a description of all methods, materials and conditions for the conduct of the study.

j) The dose levels and/or concentration(s), frequency, duration and method of administration of the test, control or reference substance.

k) The route of administration, where applicable, and the reason for its choice.

l) The type and frequency of tests, analyses, measurements, observations and examinations, where applicable.

m) A description of the randomisation scheme and proposed statistical methods.

n) The records to be maintained.

o) The date of approval of the study plan by the sponsor, and the signature of the Study Director.

The study plan shall be retained as raw data. All changes, modifications, or revisions to an approved study plan and reasons therefore shall be documented, signed by the Study Director, dated and maintained with the study plan.

G. 2. CONDUCT OF A STUDY

a) The Study Director shall be made responsible for supervising the study in a manner which will provide for the accuracy of the data and findings generated during the study, and for their documentation.

b) The study has to be conducted in accordance with the study plan. If deviations from the study plan seem necessary, the Study Director must review them, approve them with signature and date, and give written justification of them.

c) All data generated and procedures followed during the conduct of a study, except those that are generated as direct computer input, shall be recorded directly, promptly, accurately and legibly by the person entering the data, and shall be signed or initialed, and dated. Any change in the raw data shall be made so as not to obscure the previous entry, and if necessary shall indicate the reason for change and shall be identified by date and signature of the person making the change. Data generated as direct computer input shall be identified at the time of data input by the person(s) responsible for direct data entries. Corrections must be identified separately by the responsible person(s), shall indicate the reason for change, and shall be dated.

SUB-PART J : RECORDS AND REPORTS

J. 1. REPORTING OF STUDY RESULTS

a) A final report shall be prepared for each study and shall include, but not be limited to, the following :

   i) All information and data laid down in the approved study plan, and the changes in, or revisions of, the approved plan.

   ii) A description of all known circumstances which may have affected the quality and integrity of the study.

   iii) The name of the Study Director and of other scientists or professionals involved in the study.

   iv) A description of the transformations, calculations or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.

   v) The signed and dated report of the principal scientist from each of the cooperating disciplines involved in the study.

   vi) The locations where the specimens, raw data and final reports are to be stored.

   vii) The statement prepared and signed according to the Quality Assurance procedure as in B.4 a). v).

b) The final report shall be signed by the Study Director.

c) Corrections and additions to a final report shall be in the form of an amendment. The amendment shall clearly specify the reason for the corrections or additions, and be signed and dated by the Study Director and by the principal scientist from the discipline involved, if necessary.

J. 2. STORAGE AND RETRIEVAL OF RECORDS AND DATA

a) There shall be archives for the storage of the study plans, raw data, specimens and final reports. Materials retained in the archives shall be indexed so as to facilitate orderly storage and rapid retrieval.

b) An individual shall be identified as responsible for the archives, and he shall permit access to the archives only to authorised personnel.

J. 3. RETENTION OF RECORDS

a) The study plan, raw data, specimens and final report of each study : records of all audits as specified by paragraph B.4.b) ; summaries of qualifications, training, experience and job descriptions of personnel as specified in paragraph B. 2. b) ; records and reports of the maintenance and calibration of equipment as specified in paragraph D. 2. ; the historical file of standard operating procedures as specified in paragraph E. 1. ; and samples of test, control and reference substances as specified in paragraph F. 1. a) shall be retained for the period specified by the competent authority.

b) Specimens and samples shall be retained only as long as the quality of the preparation permits evaluation.

c) If a facility having conducted a study goes out of business, the material required to be stored as specified in paragraph J. 2. a) shall be transferred to the archives of the sponsor of the study.

APPENDIX I : MEMBERS OF ECETOC

BELGIUM

COLGATE-PALMOLIVE, Herstal
ESSOCHEM EUROPE, Brussels
MONSANTO EUROPE, Brussels
PROCTER & GAMBLE, Brussels
SOLVAY, Brussels

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ATO CHIMIE, Paris
CDF CHIMIE, Paris
PRODUITS CHIMIQUES UGINE KUHLMANN, Paris
RHONE-POULENC, Paris

GERMANY

BASF, Ludwigshafen
BAYER, Leverkusen
CHEMISCHE WERKE HÜLS, Marl
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DYNAMIT NOBEL, Troisdorf
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HOECHST, Frankfurt
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RÜTGERS, Duisburg
VEBA OEL, Gelsenkirchen
WACKER CHEMIE, Munich

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ANIC, Milan
MONTEDISON, Milan

NETHERLANDS

AKZO, Arnhem
DSM, Heerlen
PHILIPS-DUPHAR, Weesp
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NORSK HYDRO, Oslo

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ASTRA PHARMACEUTICALS, Södertälje
KEMANOBEL, Stockholm

SWITZERLAND

CIBA-GEIGY, Basel
DOW CHEMICAL EUROPE, Horgen
HOFFMANN-LA ROCHE, Basel
SANDOZ, Basel

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ALBRIGHT & WILSON, London
BP CHEMICALS, London
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J. P. TASSIGNON, Counsellor, Industrial Medicine and Toxicology	SOLVAY (Brussels)
H. G. VAN RAALTE, Consultant Toxicologist	SHELL (Den Haag)

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H. ZELLER (vice chairman), Head of Dept. Industrial Hygiene and Toxicology	BASF (Ludwigshafen)
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B. BROECKER, Coordinator product-related environmental problems	HOECHST (Frankfurt)
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